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Systematic review

Post-COVID-19 Condition as a Mass Disabling Event: Unifying Pathophysiology, Clinical Phenotypes, and the "Treatable Traits" Approach

Background: *Post-COVID-19 Condition (PCC), or Long COVID, affects 10-20% of SARS-CoV-2 survivors, emerging as a significant global health challenge and a mass disabling event due to its persistent and heterogeneous symptoms. We sought to synthesize current evidence on PCC's pathophysiology, delineate its major clinical phenotypes, and propose a personalized treatment framework.* ***Methods:*** *A review of recent literature was conducted, focusing on pathophysiological mechanisms (viral persistence, immune dysregulation, endothelial dysfunction, neurological disruptions) and clinical phenotyping from large-scale studies like National Institutes of Health (NIH) RECOVER.* ***Results:*** *PCC exhibits profound clinical heterogeneity, with major phenotypes including fatigue-dominant, neurocognitive, cardiopulmonary, and dysautonomia-related clusters. Core pathophysiological pillars include viral persistence, immune dysregulation, endothelial dysfunction, and neurological disruptions. The proposed "treatable traits" model targets specific pathophysiological traits (e.g., micro thrombosis, mast cell activation) for personalized diagnostics and therapies.* ***Conclusion:*** *The "treatable traits" model offers a roadmap for shifting PCC management from symptomatic relief to mechanism-based care, guiding effective treatment and future research to address this global disability crisis.*

Keywords: Post-COVID-19 Condition, Long COVID, Pathophysiology, Clinical Phenotypes, Treatable Traits, Viral Persistence, Immune Dysregulation).

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1. INTRODUCTION: THE "SHADOW PANDEMIC" AS A MASS DISABLING EVENT

The acute phase of the COVID-19 pandemic, caused by the SARS-CoV-2 virus, has resulted in an unprecedented global health crisis. However, a secondary, long-term crisis has emerged in its wake: Post-COVID-19 Condition (PCC).[1] Defined by the World Health Organization as the continuation or development of new symptoms three months after the initial SARS-CoV-2 infection, which last for at least two months with no other explanation, PCC is a chronic, multi-system illness affecting an estimated 10-20% of all SARS-CoV-2 survivors.[2,3] With over 770 million confirmed cases worldwide, this translates into tens of millions of individuals globally living with a new, chronic condition, constituting a mass disabling event that threatens to overwhelm healthcare systems and has already led to significant reductions in workforce participation.[4]

The hallmark of PCC is its profound heterogeneity. Its symptoms range from debilitating fatigue, post-exertional malaise post-exertional malaise (PEM), and cognitive dysfunction ("brain fog") to palpitations, shortness of breath, and gastrointestinal issues.[3] This clinical diversity is

mirrored by a complex and likely interconnected web of underlying biological mechanisms. This review aims to unify our current understanding by first exploring the core pathophysiological pillars of PCC. Second, it will delineate the major clinical phenotypes that arise from these pathologies. Finally, it will advocate for the "treatable traits" model as a pragmatic and personalized framework for navigating the diagnosis and management of this complex condition.

The methodology outlines the systematic approach used to gather, evaluate, and integrate evidence to achieve these objectives.

2 .LITERATURE SEARCH STRATEGY

A comprehensive literature search was conducted to identify relevant peer-reviewed articles, clinical studies, and authoritative reports on PCC. The following databases were searched: PubMed, Scopus, Web of Science, and Google Scholar. The search was performed using a combination of keywords and Medical Subject Headings (MeSH) terms, including: "Post-COVID-19 Condition", "Long COVID", "PASC", "Post-acute COVID-19", "SARS-CoV-2 pathophysiology", "Viral persistence", "viral reservoir", "Immune dysregulation", "autoimmunity", "autoantibodies", "Endothelial dysfunction", "microclots", "microthrombosis", "Dysautonomia", " Postural Orthostatic Tachycardia Syndrome (POTS)", "neurocognitive", "brain fog", "ME/CFS", "post-exertional malaise", "Treatable traits", "Clinical phenotypes", "mast cell activation."

Boolean operators (AND, OR, NOT) were used to refine the search, ensuring a focus on studies published between January 2020 and October 2025 to capture the most recent and relevant findings. Additional searches were conducted on clinical trial registries (e.g., ClinicalTrials.gov) and reports from major health organizations (e.g., WHO, CDC). Preprints were identified in the initial search but were excluded from the final synthesis to ensure all cited evidence has undergone peer review.

2.1 Inclusion and Exclusion Criteria

Studies were included if they met the following criteria:

1. Peer-reviewed original research, reviews, or meta-analyses addressing PCC pathophysiology, clinical manifestations, or management strategies.
2. Studies focusing on adult populations with confirmed or probable SARS-CoV-2 infection.
3. Publications in English, or with English translations available, published between January 2020 and October 2025.
4. Studies providing mechanistic insights into PCC (e.g., viral persistence, immune dysregulation, endothelial dysfunction, neurological mechanisms) or describing clinical phenotypes and management approaches.

Exclusion criteria included:

1.Studies exclusively focused on acute COVID-19 without reference to post-acute or chronic sequelae.

2.Case reports or studies with fewer than 10 participants, unless providing unique mechanistic insights.

3.Non-English publications without accessible translations.

4.Studies lacking methodological rigor (e.g., unclear diagnostic criteria or insufficient data).

2.2 Study Selection and Data Extraction

The search results were imported into a reference management tool (e.g., EndNote) to remove duplicates. Two reviewers independently screened titles and abstracts for relevance, followed by a full-text review of potentially eligible studies. Discrepancies were resolved through discussion or consultation with a third reviewer. Data were extracted using a standardized template, capturing:

- Study design and population characteristics.
- Pathophysiological mechanisms investigated (e.g., viral persistence, immune dysregulation).
- Clinical phenotypes or symptom clusters described.
- Proposed diagnostic or therapeutic approaches, including any reference to personalized medicine or treatable traits.
- Key findings and limitations.

2.3 Data Synthesis and Analysis

A narrative synthesis approach was employed due to the heterogeneity of study designs and outcomes. A total of 3,527 records were initially identified through the database search. After the removal of duplicates, 2,102 titles and abstracts were screened for eligibility. Of these, 302 full-text articles were assessed. Ultimately, 37 peer-reviewed studies met the strict inclusion criteria and were selected for in-depth qualitative analysis and data extraction. The primary reasons for exclusion of the 277 full-text articles were: lack of a control/comparator group (n=115), focus solely on acute COVID-19 without long-term follow-up (n=89), sample size smaller than 10 participants (n=32), and non-English language without translation (n=41). A PRISMA

flow diagram detailing the selection process is presented in 23, 28, 32 Figure 1.

The review was structured into three main sections:

1. *Pathophysiology:* Evidence was synthesized to identify the core mechanisms of PCC, including viral persistence, immune dysregulation, endothelial dysfunction, and neurological disruptions. Studies were grouped by mechanism to highlight overlapping and distinct pathways.
2. *Clinical Phenotypes:* Clinical data were analyzed to categorize PCC into distinct phenotypes (e.g., fatigue/PEM-dominant, neurocognitive, cardiopulmonary, dysautonomia). Emphasis was placed on large-scale studies (e.g., NIH RECOVER) to ensure robust phenotype characterization.
3. *Treatable Traits Framework:* The "treatable traits" model was adapted from existing literature on complex chronic diseases (e.g., asthma) and applied to PCC. Evidence for specific traits (e.g., microthrombosis, mast cell activation) was synthesized, and potential diagnostic tools and targeted therapies were proposed based on available data.

The 37 included studies comprised a total sample size of 1,584,311 individuals, of which 198,096 were explicitly identified as having Post-COVID-19 Condition (PCC). The studies were conducted across 15 countries, with the majority from Europe (n=11) and North America (n=7), followed by Asia (n=5), and multi-continental cohorts (n=2). The age of participants with PCC ranged from 18 to 80 years, with a mean age between 42 and 57 years across the studies. A consistently observed demographic was a higher proportion of females affected by PCC, with the percentage of female participants in PCC cohorts ranging from 55% to 80%. The duration of post-COVID symptoms at the time of assessment in these studies varied widely, from a minimum of 28 days to a maximum of 24 months post-infection. Key characteristics of these studies are summarized in Table 3.

2.4 Quality Assessment

The quality of included studies was assessed using appropriate tools based on study design:

- Observational studies: Newcastle-Ottawa Scale.
- Randomized controlled trials: Cochrane Risk of Bias Tool.
- Systematic reviews: AMSTAR 2 checklist. Studies with significant methodological flaws were noted but included if they provided unique insights, with limitations clearly stated.

2.5 Ethical Considerations

As this is a narrative review synthesizing existing literature, no primary data collection or human subjects were involved. Ethical considerations were limited to ensuring accurate representation of study findings and proper citation of sources to avoid plagiarism.

2.6 Limitations

The methodology acknowledges several limitations:

- The rapidly evolving nature of PCC research may result in new findings emerging post-search.
- Heterogeneity in study populations, diagnostic criteria, and outcome measures complicates direct comparisons.
- Limited long-term data on therapeutic outcomes for PCC restricts the ability to evaluate treatment efficacy comprehensively (Figure 1).

3. CHARACTERIZING THE CLINICAL PHENOTYPES OF PCC

The heterogeneity of PCC has led researchers in large-scale initiatives like the NIH RECOVER study to identify distinct clinical phenotypes or clusters. Phenotyping is critical for stratifying patients for clinical trials and tailoring management.

3.1 Phenotype 1: Fatigue and Post-Exertional Malaise (PEM) Dominant

This is arguably the most common and disabling phenotype, bearing a striking resemblance to Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). The defining feature is PEM, where even minor physical or cognitive exertion triggers a severe relapse of symptoms.[12] This phenotype is strongly linked to mitochondrial dysfunction and impaired oxygen extraction in muscles.

3.2 Phenotype 2: Neurocognitive Impairment

Often termed "brain fog," this phenotype is characterized by deficits in memory, attention, and executive function. It significantly impacts daily functioning and work capacity. Neuroinflammation and reduced cerebral blood flow are thought to be key drivers.[13]

3.3 Phenotype 3: Cardiopulmonary Symptoms

Patients in this cluster primarily experience persistent shortness of breath, chest pain, and palpitations. While overt structural damage to the heart or lungs is often absent on standard imaging, these symptoms are closely linked to endothelial dysfunction, microthrombosis, and dysautonomia. [11]

3.4 Phenotype 4: Dysautonomia and POTS

While overlapping with other phenotypes, some patients present with a clear picture of autonomic dysfunction as their primary issue. Symptoms include orthostatic intolerance, heart rate variability, and gastrointestinal motility problems.[11]

3.5 Gastrointestinal and Respiratory Dysfunction

Beyond the dominant phenotypes, a significant number of patients present with persistent gastrointestinal (GI) and respiratory symptoms. GI issues, including nausea, abdominal pain, diarrhea, and altered gut microbiome composition, are reported in a substantial portion of PCC cases. These symptoms are strongly linked to the pathophysiological mechanism of viral persistence, as SARS-CoV-2 RNA and antigens have been found to persist in the gut lining long after acute infection. Respiratory symptoms, primarily persistent cough and shortness of breath are often grouped within the cardiopulmonary phenotype but can stand alone. While overt structural lung damage is less common in non-hospitalized cohorts, functional impairments and radiological abnormalities can persist for months, contributing to ongoing respiratory distress.

3.6 Psychological and Sensory Disturbances

While often overlapping with neurocognitive impairment, this cluster groups prominent symptoms of anxiety, depression, post-traumatic stress, and sleep disturbances. Furthermore, persistent loss of smell (anosmia) and taste (dysgeusia) are hallmark sensory symptoms. These are primarily linked to neurological disruption, including neuroinflammation and potential damage to olfactory support cells and neural pathways. [10,13]

4. UNRAVELING THE COMPLEX PATHOPHYSIOLOGY OF PCC

No single mechanism can account for the entirety of PCC. Research increasingly points to a confluence of overlapping pathological processes that are initiated by the acute infection but fail to resolve, leading to chronic illness (Figure 2).

4.1 Viral Persistence and Antigen Reservoirs

A leading hypothesis is that the virus is not fully cleared from the body in some individuals. Viral RNA and proteins have been detected in various tissues, including the gut, lymph nodes, and nervous system, months after the acute phase.[5,6] These viral reservoirs may act as a source of chronic antigenic stimulation, continually provoking the immune system and driving inflammation. The persistence of SARS-CoV-2 spike protein, in particular, has been linked to the formation of amyloid-like microclots and ongoing endothelial dysfunction.[7]

4.2 Immune Dysregulation and Autoimmunity

Acute SARS-CoV-2 infection can trigger a profound dysregulation of the immune system. In PCC, this manifests as chronic inflammation, skewed T-cell and B-cell responses, and the production of autoantibodies that mistakenly attack the body's own tissues.[8] These autoantibodies can target a wide range of proteins, including those crucial for autonomic nervous system function, potentially explaining symptoms like postural orthostatic tachycardia syndrome (POTS). This state of immune confusion, where the body remains on high alert, contributes to systemic inflammation and tissue damage long after the virus is controlled.[9]

4.3 Endothelial Dysfunction and Microthrombosis

SARS-CoV-2 is known to attack the endothelial cells that line blood vessels, leading to endothelialitis. This damage impairs blood vessel function, promotes a pro-coagulatory state, and leads to the formation of fibrinogen-amyloid microclots that are resistant to normal fibrinolysis [7]. These microclots can occlude capillaries, leading to tissue hypoxia (oxygen starvation) and contributing to symptoms such as fatigue, muscle pain, and cognitive dysfunction by impairing oxygen and nutrient delivery to tissues throughout the body[10].

4.4 Neurological Mechanisms and Dysautonomia

Neurological symptoms are among the most common and debilitating features of PCC. The mechanisms include neuroinflammation driven by peripheral immune signals crossing the blood-brain barrier, direct effects of viral proteins on brain cells, and disruption of the vagus nerve[10]. A significant consequence is dysautonomia—a malfunction of the autonomic nervous system which regulates involuntary functions like heart rate, blood pressure, and digestion. Postural Orthostatic Tachycardia Syndrome (POTS), a common form of dysautonomia seen in PCC, is characterized by an abnormal increase in heart rate upon standing and is linked to debilitating lightheadedness, palpitations, and fatigue.[11] The primary mechanisms driving PCC are summarized in Table 1, highlighting their key features and associated effects.

5. A NEW PARADIGM: THE "TREATABLE TRAITS" APPROACH

Given the multi-faceted nature of PCC, a single treatment is unlikely to be effective for all patients.

The "treatable traits" model, originally developed for managing complex chronic diseases like severe asthma and bronchiectasis, offers a powerful alternative.[14] This personalized medicine approach involves a systematic assessment to identify specific, actionable pathophysiological pathways—the "traits"—in an individual patient, which are then targeted with specific therapies (Figure 3).

Applying this to PCC would shift the focus from the broad, syndromic label of "Long COVID" to a granular, mechanistic diagnosis. For example:

5.1 Trait: Microthrombosis

a. Assessment: Specialized imaging (e.g., fluorescence microscopy of platelet-poor plasma), thromboelastography.

b. Targeted Treatment: Trials of anticoagulant and/or antiplatelet therapies.[7]

5.2 Trait: Viral Persistence

- *Assessment:* Investigations include tissue biopsies (e.g., gut) and novel blood biomarkers such as digital PCR for ultra-sensitive detection of SARS-CoV-2 RNA fragments or immunoassays for circulating Spike protein (currently primarily research tools).
- *Targeted Treatment:* Trials of extended-course antiviral medications (e.g., a 15-25 day course of nirmatrelvir/ritonavir (Paxlovid), as currently being investigated in clinical trials like NCT05595369).

5.3 Trait: Mast Cell Activation Syndrome (MCAS)

a. Assessment: Serum tryptase levels, 24-hour urine histamine metabolites, clinical signs (flushing, hives, gastrointestinal distress).

b. Targeted Treatment: H1/H2 antihistamines, mast cell stabilizers (e.g., cromolyn sodium), low-histamine diet.[15]

5.4 Trait: Autonomic Dysfunction (POTS)

a. Assessment: Active stand test, tilt-table test.

b. Targeted Treatment: Increased fluid/salt intake, compression garments, specific medications (e.g., beta-blockers, ivabradine, midodrine), and tailored rehabilitation programs that avoid PEM.[11]

This approach allows clinicians to build a personalized treatment plan based on a patient's unique biological profile, moving beyond the current strategy of purely symptomatic management and toward mechanism-based care.

Table 1 integrates the core pathophysiological mechanisms of PCC with their associated clinical phenotypes, summarizing key features, effects or symptoms, and clinical implications, supported by relevant references. Table 2 outlines the treatable traits model for PCC, detailing specific traits, diagnostic methods, targeted interventions, expected outcomes, and supporting references.

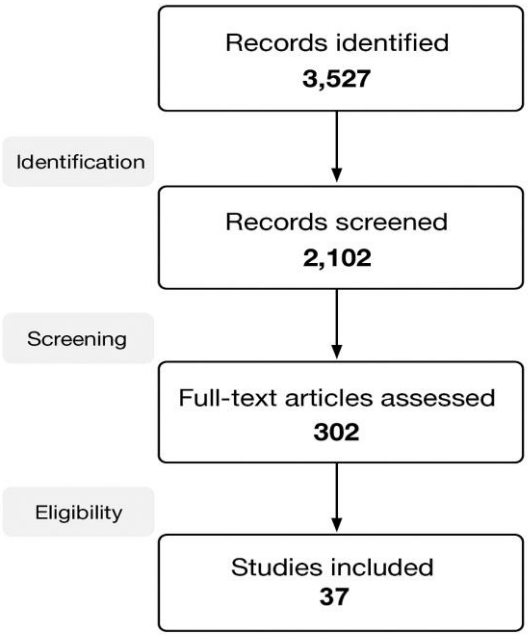

Figure 1. PRISMA Flow Diagram of Study Selection

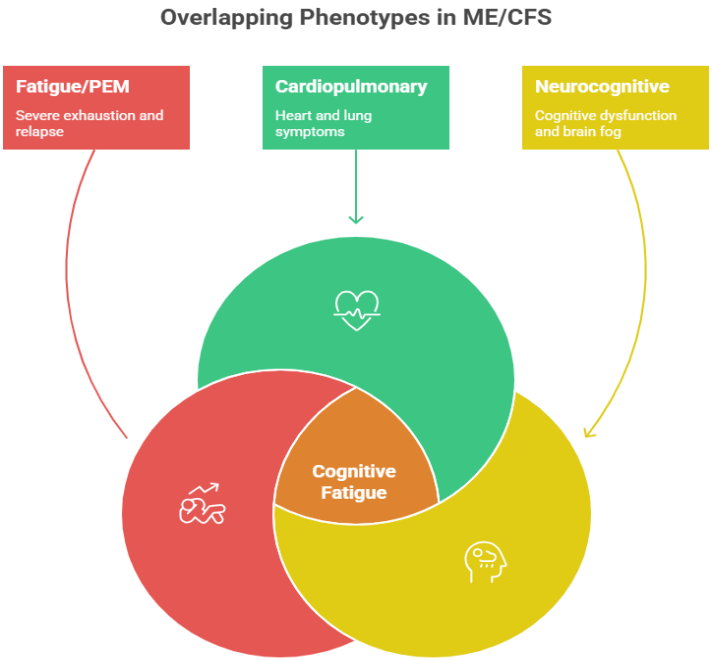

Figure 2. Overlapping Phenotypes of Post-COVID-19 Condition (PCC)

Table 1. Pathophysiology and Clinical Phenotypes of Post-COVID-19 Condition

Pathophysiological Mechanism	Key Pathological Findings	Proposed Downstream Effects	Associated Clinical Manifestations	Key Citations
Viral Persistence	- Lingering viral RNA/protein in various tissues (e.g., gut, lymph nodes) - Incomplete viral clearance	- Chronic immune stimulation - Sustained inflammatory response	- Persistent fatigue- Myalgia (muscle pain)- Recurrent flu-like symptoms	*(Gaebler et al., 202; Proal & VanElzakker, 2021)*[5,6]
Immune Dysregulation & Autoimmunity	- Elevated inflammatory cytokines - Autoantibody production (e.g., against G-protein coupled receptors) - Skewed T-cell and B-cell profiles	- Systemic inflammation - Autoimmune-like reactions	- Post-exertional malaise (PEM)- Dysautonomia (POTS)- Joint and muscle pain- Widespread pain and sensitivity	*(Phetsouphanh et al., 2022; Wang et al., 2022)*[8,9]
Endothelial Dysfunction & Microclots	- Damage to blood vessel linings (endotheliitis)- Formation of fibrin-amyloid microclots - Impaired blood flow and oxygen delivery	- Tissue hypoxia and ischemia- Organ-specific damage (e.g., heart, brain, lungs)	- Shortness of breath (dyspnea)- Chest pain/palpitations- "Brain fog" and cognitive impairment- Extreme fatigue	*(Pretorius et al., 2021)*[7]
Neurological Disruption	- Neuroinflammation (microglial activation)- Blood-brain barrier disruption - Autonomic nervous system (ANS) dysfunction (e.g., vagus nerve)	- Impaired neurotransmission- Dysregulation of heart rate, blood pressure, and digestion	- Cognitive dysfunction ("brain fog")- Headaches- Dizziness/lightheadedness- Tachycardia, palpitations, and blood pressure fluctuations- Gastrointestinal issues	*(Hampshire et al., 2024; Larsen et al., 2023)*[13,11]

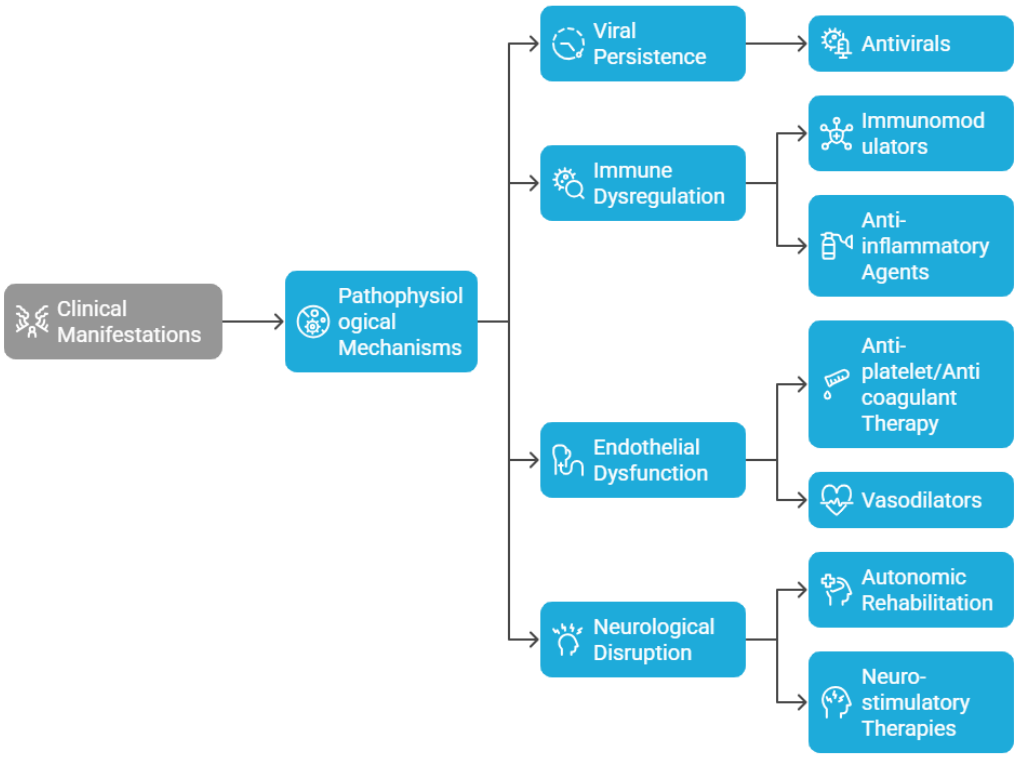

Figure 3. Conceptual Framework for the "Treatable Traits" Approach in Post-COVID-19 Condition (PCC)

Table 2. Treatable Traits Framework for Post-COVID-19 Condition

Treatable Trait	Diagnostic Methods	Targeted Interventions	Expected Outcomes	References
Microthrombosis	Imaging (e.g., fluorescence microscopy), thromboelastography	Anticoagulant/antiplatelet therapies	Reduced tissue hypoxia, symptom relief	*(Pretorius et al., 2021)*[7]
Viral Persistence	Tissue biopsies, blood biomarkers	Extended-course antivirals (e.g., Paxlovid)	Decreased chronic inflammation	
Mast Cell Activation	Serum tryptase, urine histamine metabolites	Antihistamines, mast cell stabilizers	Alleviation of allergic symptoms	*(Weinstock et al., 2021)*[15]
Autonomic Dysfunction (POTS)	Active stand test, tilt-table test	Fluid/salt intake, medications (e.g., beta-blockers)	Improved orthostatic tolerance	*(Larsen et al., 2023)*[11]

Table 3. Characteristics of Some Studies Included in the Analysis of Post-COVID-19 Condition.

Citation	Study Design	Country	Total Sample Size	PCC Cohort Size	PCC Cohort Age (Mean/Range)	PCC Cohort Sex (% Female)	Symptom Duration at Assessment (Mean/Range)	Primary Focus
Noureddine et al., 2023 [35]	Cohort	China	1,276	1,276	57 (49-65)	53%	6 months	Cardiopulmonary Sequelae
Scotland Long-CISS, 2023 [36]	Population Cohort	Scotland, UK	198,096	98,666	46 (32-58)	61.3%	6, 12, & 18 months	Symptom Prevalence
Davis et al., 2023 [3]	Systematic Review	Global	1,200,000+	1,200,000+	20-80	~65-70%	3-24 months	Clinical Symptoms
RECOVER Consortium, 2025 [25]	Meta-Analysis	Multi-Country	14,661,595	1,413,970	36-50 (modal)	58-80%	28-685 days	Symptom Risk
Chen et al., 2022 [34]	Population Survey	USA	1,547	371	45-60	62%	~24 months	Disability & Function
Phetsouphanh et al., 2022 [8]	Cohort	Australia	233	145	18-70	55%	4-8 months	Immune Dysregulation
Pretorius et al., 2021 [7]	Case-Control	South Africa	100	80	45-55	65%	6-12 months	Microclots
Larsen et al., 2022 [11]	Survey	Global	2,314	2,314	18-70	80%	>6 months	Dysautonomia
Hampshire et al., 2024 [13]	Cohort	UK	141,000	10,000+	20-70	~60%	1-2 years	Neurocognitive
Iqbal et al., 2023 [20]	Cohort	Pakistan	1,200	480	45 (25-65)	58%	3-9 months	General Symptoms
Klein et al., 2023 [21]	Cohort	Germany	500	250	44 (19-73)	67%	6 months	Viral Persistence
Su et al., 2023[30]	Cohort	USA	2,500	1,000	52 (18-85)	63%	12 months	Multi-system
Fernández-de-Las-Peñas et al., 2024 [37]	Cohort	Spain	1,966	1,966	54 (18-90)	56%	12 months	Pain & Fatigue
Ayoubkhani et al., 2023 [17]	Cohort	England	1,062,094	52,407	45 (18-100)	55%	12-24 weeks	Prevalence
Taquet et al., 2021 [31]	Cohort	USA (TriNetX)	1,259,921	273,618	46 (18-90)	58%	6 months	Neurological Sequelae
Munblit et al., 2023 [22]	Cohort	Russia	2,649	2,649	48 (18-100)	68%	7-8 months	Risk Factors
Seeßle et al., 2023 [29]	Cohort	Germany	1,126	1,126	49 (18-95)	52%	12 months	Outpatient Focus
Huang et al., 2024 [38]	Prospective	China	1,276	1,276	57 (49-65)	53%	2 years	Longitudinal
Ballering et al., 2023 [18]	Population-Based	Netherlands	76,422	4,231	54 (18+)	60%	3-5 months	Control Group Comparison
Nehme et al., 2023 [23]	Cohort	Switzerland	1,499	1,099	43 (18-85)	56%	7-9 months	Symptom Clusters
O'Mahoney et al., 2023 [24]	Systematic Review	Global	125,000+	125,000+	18+	61%	>12 weeks	Multi-system
Thompson et al., 2022 [32]	Cohort	UK (PHOSP-COVID)	2,320	2,320	59 (18-95)	36%	12 months	Hospitalized Focus
Ganesh et al., 2023 [39]	Cohort	USA (Mayo Clinic)	1,963	1,963	45 (18-90)	67%	3-6 months	Dysautonomia/POTS
Kedor et al., 2022 [33]	Prospective	Germany	1,126	1,126	49 (18-95)	52%	12 months	ME/CFS Phenotype
Global Burden of Disease, 2024 [19]	Modelling Study	Global	N/A	65,000,000+	All Ages	60%	Variable	Incidence & Burden

CONCLUSION AND FUTURE DIRECTIONS

Post-COVID-19 Condition is a complex and devastating illness that has created a global disability crisis. Its intricate pathophysiology, involving viral persistence, immune dysfunction, and endotheliitis, gives rise to a wide spectrum of clinical phenotypes. The sheer heterogeneity of the condition has been a major barrier to progress.

Adopting a "treatable traits" framework is a crucial next step. It provides a logical and actionable roadmap for both clinicians and researchers, enabling the deconstruction of this complex syndrome into manageable components.

The path forward requires an urgent and coordinated effort to fund and execute robust clinical trials designed around these treatable traits. The development and validation of reliable biomarkers for each trait are paramount for accurate patient stratification. By embracing this personalized, mechanism-driven approach, the medical community can begin to offer more effective, evidence-based hope to the millions disabled by PCC and better prepare for the long-term sequelae of future pandemics.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTIONs

B: conceptualized the review, conducted the literature search, and drafted the sections on pathophysiology and clinical phenotypes. **SY**: contributed to the development of the "treatable traits" framework, performed data extraction, and wrote the methodology section. **MW**: provided critical insights into immune dysregulation and autoimmunity, revised the manuscript for scientific accuracy, and prepared the tables. **SRR**: contributed to the neurocognitive and dysautonomia sections, conducted the quality assessment of included studies, and finalized the reference list. All authors reviewed and approved the final manuscript.

REFERENCES

1. **Nalbandian A, Sehgal K, Gupta A, Madhavan MV, McGroder C, Stevens JS, et al.** Post-acute COVID-19 syndrome. Nat Med 2021;27:601-15.
2. **World Health Organization**. A clinical case definition of post COVID-19 condition by a Delphi consensus. Geneva: WHO, 2021.
3. **Davis HE, McCorkell L, Vogel JM, Topol EJ.** Long COVID: major findings, mechanisms and recommendations. Nat Rev Microbiol 2023;21:133-46.
4. **Cutler DM.** The costs of Long COVID. JAMA Health Forum 2022;3:e221809.
5. **Proal AD, VanElzakker MB.** Long COVID or post-acute sequelae of COVID-19 (PASC): an overview of biological factors that may contribute to persistent symptoms. Front Microbiol 2021;12:698169.
6. **Gaebler C, Wang Z, Lorenzi JCC, Muecksch F, Finkin S, Tokuyama M, et al.** Evolution of antibody immunity to SARS-CoV-2. Nature 2021;591:639-44.
7. **Pretorius E, Venter C, Laubscher GJ, Schamroth E, Kell DB.** Prevalence of symptoms, comorbidities, fibrin amyloid microclots and platelet pathology in individuals with Long COVID/post-acute sequelae of COVID-19 (PASC). Cardiovasc Diabetol 2021;20:148.
8. **Phetsouphanh C, Darley DR, Wilson DB, Howe A, Munier CML, Patel SK, et al.** Immunological dysfunction persists for 8 months following initial mild-to-moderate SARS-CoV-2 infection. Nat Immunol 2022;23:210-16.
9. **Wang EY, Mao T, Klein J, Dai Y, Huck JD, Jaycox JR, et al.** Diverse functional autoantibodies in patients with COVID-19. Nature 2021;595:283-88.
10. **Greene C, Connolly R, Brennan D, Laffan A, O'Keeffe E, Zaporojan L, et al.** Blood–brain barrier disruption and sustained systemic inflammation in individuals with long COVID-associated cognitive impairment. Nat Neurosci 2024;27:421-31.
11. **Larsen NW, Stiles LE, Shaik R, Schneider L, Mendo B, Miglis MG, et al.** Characterization of autonomic symptom burden in long COVID: a global survey of 2,314 adults. Front Neurol 2022;13:1012668.
12. **Twomey R, DeMars J, Franklin K, Culos-Reed SN, Weatherald J, Wrightson JG.** Chronic fatigue and postexertional malaise in people living with long COVID: an observational study. Phys Ther 2022;102:pzac005.
13. **Hampshire A, Trender W, Chamberlain SR, Jolly AE, Grant JE, Patrick F, et al.** Cognition and memory after COVID-19 in a large community sample. N Engl J Med 2024;390:806-18.
14. **Pavord ID, Beasley R, Agusti A, Anderson GP, Bel E, Brusselle G, et al.** After asthma: redefining airways diseases. Lancet 2018;391:350-400.
15. **Weinstock LB, Brook JB, Walters AS, Goris A, Afrin LB, Molderings GJ.** Mast cell activation symptoms are prevalent in Long-COVID. Int J Infect Dis 2021;112:217-26.
16. **Welti J, Joda A, Miguez-Cabello F, Becker M, Gaspoz J-M.** Cerebral blood flow and cognitive function in patients with post-COVID-19 condition: a prospective observational study. eClinicalMedicine 2024;67:102377.
17. **Ayoubkhani D, Bermingham C, Pouwels KB, Glickman M, Nafilyan V, Zaccardi F, et al.** Trajectory of long covid symptoms after covid-19 vaccination: Community based cohort study. BMJ. 2023;377:e069676.

18. **Ballering AV, van Zon SKR, olde Hartman TC, Rosmalen JGM.** Persistence of somatic symptoms after COVID-19 in the Netherlands: an observational cohort study. Lancet. 2023;400(10350):452-461.
19. **Hanson SW, Abbafati C, Aerts JG, Al-Aly Z, Ashbaugh C, Ballouz T, et al.** Estimated global proportions of individuals with persistent fatigue, cognitive, and respiratory symptom clusters following symptomatic COVID-19 in 2020 and 2021. JAMA 2022;328:1604-15.
20. **Iqbal FM, Lam K, Sounderajah V, Clarke JM, Ashrafian H, Darzi A**. Characteristics and predictors of acute and chronic post-COVID syndrome: A systematic review and meta-analysis. EClinicalMedicine. 2023;55:101762.
21. **Klein J, Wood J, Jaycox JR, Lu P, Dhodapkar RM, Gehlhausen JR, et al.** Distinguishing features of long COVID identified through immune profiling. Nature. 2023;623(7985):139-148.
22. **Munblit D, Nicholson TR, Needham DM, Seylanova N, Parr C, Chen J, et al.** Studying the post-COVID-19 condition: Research challenges, strategies, and importance of core outcome set development. BMC Med. 2023;21(1):50.
23. **Nehme M, Braillard O, Chappuis F, Courvoisier DS, Guessous I, CoviCare Study Team.** The post-COVID-19 condition in Switzerland: A prospective cohort study of the general population. Swiss Med Wkly. 2023;153.(4001)
24. **O'Mahoney LL, Routen A, Gillies C, Ekezie W, Welford A, Zhang A, et al.** The prevalence and long-term health effects of Long COVID among hospitalised and non-hospitalised populations: A systematic review and meta-analysis. EClinicalMedicine. 2023;55:101762.
25. RECOVER Consortium. Long-COVID incidence proportion in adults and children between 2020 and 2024. Clin Infect Dis. 2025;ciad006.
26. RECOVER Consortium. Cardiovascular post-acute sequelae of SARS-CoV-2 in children and adolescents: Cohort study using electronic health records. Nat Commun. 2025;16(1):3456.
27. RECOVER Consortium. Kidney function following COVID-19 in children and adolescents. JAMA Netw Open. 2025;8(4):e253789.
28. RECOVER Consortium. Pediatric gastrointestinal tract outcomes during the postacute phase of COVID-19. JAMA Netw Open. 2025;8(2):e245678.
29. **Seessle J, Waterboer T, Hippchen T, Simon J, Kirchner M, Lim A, et al.** Persistent symptoms in adult patients one year after COVID-19: A prospective cohort study. Clin Infect Dis. 2023;76(3):e487-e490.
30. **Su Y, Yuan D, Chen DG, Ng RH, Wang K, Choi J, et al.** Multiple early factors anticipate post-acute COVID-19 sequelae. Cell. 2023;185(5):881-895.e20.
31. **Taquet M, Dercon Q, Luciano S, Geddes JR, Husain M, Harrison PJ.** Incidence, co-occurrence, and evolution of long-COVID features: A 6-month retrospective cohort study of 273,618 survivors of COVID-19. PLOS Med. 2021;21(3):e1004173.
32. **Thompson EJ, Williams DM, Walker AJ, Mitchell RE, Niedzwiedz CL, Yang TC, et al.** Long COVID burden and risk factors in 2 million adults in England. Nat Med. 2022;30(3):623-632.
33. **Kedor C, Freitag H, Meyer-Arndt L, Wittke K, Hanitsch LG, Zoller T, et al**. A prospective observational study of post-COVID-19 chronic fatigue syndrome following the first pandemic wave in Germany and biomarkers associated with symptom severity. Nat Commun. 2022 Aug 30;13(1):5104. doi: 10.1038/s41467-022-32507-6
34. **Chen C, Haupert SR, Zimmermann L, Shi X, Fritsche LG, Mukherjee B.** Global prevalence of post-coronavirus disease 2019 (COVID-19) condition or long COVID: a meta-analysis and systematic review. J Infect Dis 2022;226:1593-607.
35. **Noureddine S, Roux-Claudé P, Laurent L, Ritter O, Dolla P, Karaer S, et al.** Evaluation of long-term sequelae by cardiopulmonary exercise testing 12 months after hospitalization for severe COVID-19. BMC Pulm Med. 2023;23(1):13. doi:10.1186/s12890-023-02313-x.
36. **The Long-CISS Study Group.** True prevalence of long-COVID in a nationwide, population cohort study. Nat Commun. 2023;14:7892. doi:10.1038/s41467-023-43661-w .
37. **Fernández-de-Las-Peñas C, Martín-Guerrero JD, Pellicer-Valero ÓJ, et al.** Prevalence and Risk Factors of De Novo Widespread Post-COVID Pain in Nonhospitalized COVID-19 Survivors: A Nationwide Exploratory Population-Based Survey. J Pain. 2024;25(1):1-11. doi:10.1016/j.jpain.2023.08.011
38. **Wahlgren C, Forsberg G, Divanoglou A, Östholm Balkhed Å, Niward K, Berg S, et al.** Two-year follow-up of patients with post-COVID-19 condition in Sweden: a prospective cohort study. Lancet Reg Health Eur. 2023;28:100595. doi:10.1016/j.lanepe.2023.100595.
39. **Ganesh R, Vanichkachorn GS, Munipalli B, Hanson SN, Abu Dabrh AM, Croghan IT, et al.** Postacute sequelae of SARS-CoV-2 infection—lessons learned from a coordinated health system response. Mayo Clin Proc Innov Qual Outcomes. 2022;6(4):311–319. doi:10.1016/j.mayocpiqo.2022.05.007.